REMARKS

After entry of this amendment, claims 1, 3-5, 7-33, 35-36 and 38-45 are pending.

35 U.S.C. § 112 Rejections

Further reconsideration is respectfully requested of the rejection of claims 1, 3-33 and 35-45 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. As explained below, applicant respectfully maintains that the pending claims are fully enabled. The Office states that the "specification does not enable any person skilled in the art to which it pertains, ... to use the invention commensurate in scope with these claims."[1] The Examiner asserts that "treat" is understood as "providing a cure or relief of an existing condition."[2] However, the Examiner cites a general purpose dictionary for the definition of this term. The Court of Appeals for the Federal Circuit in Phillips v. AWH Corp.[3] held that the "ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention ...."[4] With this in mind, a person of ordinary skill would have been likely to refer to a technical dictionary rather than a general purpose dictionary. Thus, as defined in a medical dictionary, "treatment" encompasses practices which are either prophylactic or ameliorative. For example, as defined in The Signet/Mosby Medical Encyclopedia, C.V. Mosby, New York (1987) treatment is

> "1. the care and overseeing of a patient to fight, reduce or prevent a disease, disorder or injury. 2. a method of fighting, reducing or preventing a disease, disorder or injury. Treatment may be pharmacologic, using drugs; surgical, involving surgery; or supportive, building the patient's strength."[5]

---

[1] Page 2 of the Office action dated May 24, 2005.

[2] Page 2 of the Office action dated May 24, 2005.

[3] Phillips v. AWH Corp., 75 U.S.P.Q.2d 1321 (Fed. Cir. 2005).

[4] See id.

[5] See pp. 584-585. The definition proceeds to discuss Conservative, Empiric, Expectant, Palliative, Preventive, Prophylactic or Rational treatments. Preventive

When read in the context of the claims and specification as a whole, and the understanding of the term "treatment" in the medical arts, the meaning of preventing or treating ototoxicity is to administer the otoprotective agent of the invention to a subject in need thereof; this administration could be prior to, simultaneous with or subsequent to the onset of ototoxicity. In any event, neither "treating" nor "relief" requires a cure, and "treating" at least is not limited to care of an existing condition.

Moreover, the Office's assertion that the application does not contain data for "treating" ototoxicity caused by either a platinum-coordination compound or an aminoglycoside is erroneous. The data in the specification demonstrates that D-methionine is effective against ototoxicity caused by platinum-coordination compounds. A person of ordinary skill would have understood from applicant's specification that to treat ototoxicity the otoprotective agent can be administered prior to, simultaneous with or subsequent to the administration of a platinum-coordination compound. Further to the skilled artisan's understanding, the authorities establish that a specification that contains a teaching of the manner and process of making and using the invention which corresponds in scope to the claims is presumed to be enabled unless there is reason to doubt the objective truth of the statements contained in the specification.[6] In this case, there is no evidence or reasoning to doubt the specification's teachings, in fact, as described below, evidence supports the accuracy of applicant's teaching.

For example, administration of a platinum-coordination compound or an aminoglycoside antibiotic to a patient can result in the generation of free radicals (or reactive oxygen species); these species can cause cellular damage. Specifically, CDDP administration increased lipid peroxidation.[7] This lipid peroxidation could be caused by CDDP's inactivation of the glutathione free radical scavenging system

---

Treatment is described as "designed to keep a disease from occurring or a mild disorder from becoming more severe." Prophylactic Treatment is further described as "for the prevention of a disease or disorder."

[6] In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971).

[7] Ravi R., Somani S., Rybak L. (1995). Mechanism of CDDP Ototoxicity: Antioxidant System. *Pharmacology and Toxicology*. 76:386-394.

because CDDP administration reduces glutathione levels and reduces activity of glutathione peroxidase and glutathione reductase. To combat the effects of free radicals, cells have multiple mechanisms for terminating free radicals. These mechanisms include endogenous antioxidants (*e.g.*, vitamins E and A, ascorbic acid, glutathione, etc.), and a series of enzymes acting as free radical scavenging systems (*e.g.*, catalase, superoxide dismutases, glutathione peroxidase, glutathione reductase). Reaction of free radicals with healthy tissue is damaging, thus, a balance between free radical formation and termination over time is important. With respect to timing, free radical processes damaging to cells must be interrupted before they become irreversible and cause cell death. More specifically, dominance of free radical formation over free radical termination can be tolerated for a finite period without damage to organ tissue; provided that, before processes leading to cell death become irreversible, the adverse effect of free radicals is interrupted by certain agents effective for the purpose, including free radical scavengers. In this way, cell death from free radical processes can be avoided.

Applicant teaches that methionine is effective for preventing cell death in the auditory system upon administration of platinum-coordination compounds and aminoglycoside antibiotics, and thus, acts as an otoprotective agent. These teachings have been corroborated by literature studies published after applicant's priority date. In one study, methionine was shown to be a free radical scavenger that increases intracellular reduced glutathione.[8] Because methionine can increase cellular glutathione levels, and can prevent the efflux of cellular glutathione secondary to injury,[9] methionine administration may increase overall cellular, including cochlear, glutathione levels. Thus, methionine aids the cell's defenses against oxidative cell damage by positively influencing the balance between free radical formation and free radical termination, and interrupting the processes that could lead to cell death. Thus, the evidence available to the art essentially corroborates the teachings of the instant

---

[8] Lu S. (1998). Regulation of Hepatic Glutathione Synthesis. *Sem in Liver Dis.* 18:331-334.

[9] Ghibelli L, Fanelli C, Rotilio G, Lafavia E, Coppola S, Colussi C, Civitareale P, Ciriolo MR. (1998). Rescue of cells from apoptosis by inhibition of active GSH extrusion. *FASEB Journal.* 12(6):479-86.

application regarding the effectiveness of methionine against ototoxicity as caused by administration of platinum-coordination compounds and ototoxicity as caused by administration of aminoglycoside antibiotics.

Moreover, given the demonstrated effectiveness of D-methionine against ototoxicity as caused by administration of platinum-coordination compounds, and the role of methionine in antioxidant mechanisms, a person of ordinary skill would have understood from applicant's disclosure that methionine can be used during the period before cell death processes become irreversible (up to at least several hours after administration of a platinum-coordination compound or aminoglycoside antibiotic) to treat cisplatin- and aminoglycoside antibiotic-induced ototoxicity. The Office has not provided any evidence or reasoning that contradicts applicant's teachings, thus, the effectiveness of methionine for treating ototoxicity resulting from administration of platinum-coordination compounds and aminoglycoside antibiotics must be accepted as valid.

35 U.S.C. § 102 Rejection – Anticipation by U.S. Patent No. 5,466,678

Reconsideration is respectfully requested of the rejection of claims 1, 6-9, 15-26 and 31-32 as being anticipated by U.S. Patent No. 5,466,678 (Kowabata et al.). Kowabata et al. disclose administration of S-adenosyl-L-methionine to reduce nephrotoxicity of a platinum complex. The claims have been amended to delete S-adenosyl methionine as an otoprotective agent. The structure contained in claim 1 does not encompass S-adenosyl methionine because the structure has two groups attached to the sulphur atom and does not allow for an adenosyl group in addition to the two alkyl groups attached to the sulfur atom. Thus, the amended claims do not include S-adenosyl methionine as an otoprotective agent and accordingly, claims 1, 7-9, 15-26 and 31-32 are not anticipated by U.S. Patent No. 5,466,678 (Kowabata et al.).

35 U.S.C. § 102 and § 103 Rejections Over Campbell et al.

Reconsideration is respectfully requested of the rejection of claims 1, 3-4, 7 and 15-18 as anticipated by Campbell et al. under 35 U.S.C. § 102 and claims 8-14 and 19-32 as being unpatentable over Campbell et al. under 35 U.S.C. § 103. The Campbell reference was published in the December, 1996 issue of Hearing Research. The

publisher mailed the December, 1996 issue on December 12, 1996 and the issue was received by at least one recipient on December 16, 1996. Because the claims uder rejection have a priority date of October 3, 1996, the Campbell et al. reference is not statutory prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103. Accordingly, claims 1, 3-4, 7 and 15-18 are not anticipated by Campbell et al. and claims 8-14 and 19-32 are not unpatentable in view of Campbell et al.

Double Patenting Rejection Obviated

Reconsideration is requested of the rejection of claims 1-45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of Campbell (U.S. Patent No. 6,187,817) and claims 1-25 of Campbell (U.S. Patent No. 6,265,386). Applicant's attorney has filed simultaneously herewith a terminal disclaimer with respect to the '817 and '386 patents. Accordingly, the obviousness-type double patenting rejection is traversed with respect to the '817 and '386 patents.

Information Disclosure Statement

References 8, 22, 34-37, 64 and 66 of the Information Disclosure Statement for the above referenced case were resubmitted with the response in U.S. Application Serial No. 10/694,432.

SIU 7398
PATENT

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge $575.00 to Deposit Account No. 19-1345 ($510.00 for a three month extension of time; and $65.00 for the government fee for filing a Terminal Disclaimer). The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

Janet S. Hendrickson, Ph.D., Reg. No. 55,258
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

JSH/dep

Mail Stop Amendment
Via Facsimile No. 571-273-8300